

## Tolerance of baked milk in patients with cow's milk-mediated eosinophilic esophagitis

To the Editor:

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease limited to the esophagus and most often triggered by food allergens.<sup>1</sup> Cow's milk is one of the most common foods causing EoE.<sup>2,3</sup> Elimination of cow's milk protein from the diet is an effective nonpharmacologic treatment of cow's milk-mediated EoE (CMME).<sup>3,4</sup> Adherence to such a diet is challenging because milk protein is present in many processed foods. In addition, strict milk restriction may have negative effects on nutrition<sup>5</sup> and quality of life.<sup>6</sup> It was recently reported that approximately 75% of children with IgE-mediated immediate hypersensitivity to cow's milk tolerate baked milk products (eg, muffins, cakes, and breads),<sup>7</sup> but it is not known whether baked milk ingestion is tolerated in patients with CMME. At our center, we identified individuals with CMME who had elected to ingest baked milk in significant quantities for at least 6 weeks and from whom we had unambiguous follow-up endoscopic data.

We used the *International Classification of Diseases, Ninth Revision*, code 530.13 (eosinophilic esophagitis) to identify patients seen at the Massachusetts General Hospital Food Allergy Center from October 2008 to April 2013 for chart review. Patients were included for analysis only if they had a definitive diagnosis of EoE and cow's milk was unambiguously implicated in disease by resolution of esophageal eosinophilia with dairy removal, or recurrence on dairy reintroduction, or both. Patients were diagnosed with EoE if 1 or more of their esophageal biopsies showed more than 15 eosinophils/hpf despite treatment with high-dose proton pump inhibitor for at least 4 weeks. Only patients with documented ingestion of at least 3 to 4 servings per week of home-baked and/or store-bought baked milk products for at least 6 weeks were included. Examples include bread, muffins, cakes, and brownies. Ingestion of cheese, even if baked (eg, pizza), was not regarded as baked milk for the purposes of this study. For inclusion, endoscopic esophageal biopsies obtained on a baked milk diet had to include at least 2 samples each from proximal, middle, and distal locations. The primary end point for analysis was histological remission during baked milk ingestion, as defined by peak eosinophil count of less than 10/hpf in all biopsies. All patients remained on proton pump inhibitor twice a day throughout the elimination and subsequent challenge, though this was not an inclusion criterion. Data were expressed as medians and interquartile ranges and were analyzed by using Mann-Whitney *U* test. A probability value of less than 5% was considered significant. This study was approved by the Partners Institutional Review Board.

A total of 422 patients were diagnosed with EoE by using the *International Classification of Diseases, Ninth Revision*, code 530.13. Within this group, we identified 16 patients with definitive EoE who ingested sufficient baked milk products for at least 6 weeks. Data for only 15 patients were analyzed because we could not unambiguously confirm that milk was the trigger in 1 patient (disease remission on multifood elimination including milk). None of the 15 patients was treated with swallowed or systemic steroids. All the 15 patients received a formal nutritional consultation as part of our clinical program. Baseline patient characteristics are shown in Table I. Eleven patients (73%) maintained histologic remission (<10 eosinophils/hpf), and

TABLE I. Baseline demographics

Baseline patient characteristics	Baked milk-tolerant (n = 11)	Baked milk-reactive (n = 4)	P value
Age (y)	13 (9-17)	11 (6-14)	.74
Sex (male)	7/11	4/4	.07
Peak eosinophil count/hpf at diagnosis	30 (25-50)	45 (35-50)	.64
Peripheral eosinophils/mm <sup>3</sup>	350 (150-490)	340 (210-470)	.87
Duration of disease (y)	6 (5-7)	6 (5-12)	.89
Total IgE (IU/mL)	124 (18-415)	137 (103-263)	.6
Milk skin prick test positivity	1/11	0/4	1.00
Milk patch test positivity	2/8	1/3	1.00
Milk-specific IgE >0.35 kU/L	3/10	1/3	1.00
Atopic disorders			1.00
Skin positivity to aeroallergens	6/7	1/2	
Eczema	4/11	2/4	
IgE-mediated food allergy	4/11	1/4	
Allergic rhinitis	2/11	2/4	
Asthma	4/11	0/4	

Descriptive data were presented as median (25th-75th range). The Mann-Whitney test was used to calculate the *P* value of nonparametric data, while the Fisher exact test was used to calculate the *P* value of categorical data. *P* < .05 is considered statistically significant.

4 patients had disease recurrence (≥10 eosinophils/hpf) after baked milk ingestion. Of note, 9 of the 11 patients had 0 - eosinophils/hpf in all their esophageal biopsies (complete histologic remission) while 2 patients had 3 and 6 peak eosinophils/hpf. Median peak eosinophil count/hpf at the time of diagnosis, and after milk elimination, milk reintroduction, and baked milk introduction are shown in Fig E1 (in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)).

After baked milk ingestion, 10 of 11 baked milk-tolerant patients had normal endoscopic findings whereas 3 of 4 baked milk-reactive patients had at least 2 abnormal endoscopic findings. One baked milk-tolerant patient with an abnormal endoscopic finding (furling) had similar findings on endoscopy with dairy elimination as well, despite complete resolution of symptoms. While eosinophilia improved on biopsy, this patient never achieved complete histologic remission with milk elimination diet or after baked milk ingestion, with peak eosinophil count of 6/hpf in both cases. None of the baked milk-tolerant patients experienced worsening of symptoms, while 3 of the 4 baked milk-reactive patients experienced mild symptom recurrence (Table II). One patient had recurrence of mild abdominal pain, and 2 patients had dysphagia. No food impactions were reported during baked milk ingestion. In this limited patient sample, skin testing, patch testing, peripheral eosinophilic count, milk-specific IgE testing, and total IgE level were not predictive of baked milk tolerance or reactivity (Table I). Patient characteristics, including age, sex, duration of disease, and frequency of other atopic disorders, were also similar between groups.

Of the 11 patients who had histologic remission after baked milk ingestion, 10 continue to remain asymptomatic while ingesting baked milk regularly. The final subject failed a second cow's milk challenge (recurrence of symptoms and esophageal eosinophilia), and subsequently, dairy intake was limited to baked milk only (mean follow-up time, 8.5 months; range, 1-17 months).

**TABLE II.** Symptoms and endoscopic findings of patients who are baked milk–tolerant (T) and baked milk–reactive (R) at baseline (left column), after at least 6 weeks of milk restriction (middle column), and after 6 weeks of baked milk ingestion (right column)

	At baseline		Off milk		Baked milk	
	T (n = 11)	R (n = 4)	T (n = 11)	R (n = 4)	T (n = 11)	R (n = 4)
<b>Symptoms</b>						
Feeding dysfunction	8 (73%)	3 (75%)	0%	0%	0%	0%
Vomiting	5 (45%)	2 (50%)	0%	0%	0%	0%
Abdominal pain	7 (64%)	2 (50%)	0%	0%	0%	1 (25%)
Dysphagia	5 (45%)	2 (50%)	0%	0%	0%	2 (50%)
Food impaction	3 (27%)	2 (50%)	0%	0%	0%	0%
<b>Endoscopic findings</b>						
Furrows	9 (81%)	1 (25%)	1 (9%)	0%	1 (9%)	3 (75%)
Rings	5 (45%)	2 (50%)	0%	2 (50%)	0%	2 (50%)
Whitish papules	6 (55%)	1 (25%)	0%	0%	0%	2 (50%)
Edema	4 (36%)	2 (50%)	0%	0%	0%	0%
Small-caliber esophagus	0%	1 (25%)	0%	0%	0%	0%
Stricture	9%	0%	0%	0%	0%	0%

All patients were symptomatic at baseline and had abnormal endoscopic findings. Symptoms and endoscopic findings improved with milk restriction. Patients who are baked milk–reactive experienced recurrence of mild symptoms after baked milk ingestion.

EoE is thought to be caused in most people by an antigen-specific allergic immune response, but the exact mechanism remains to be defined. The destruction of conformational epitopes of cow's milk has been suggested as the underlying mechanism of baked milk tolerance in IgE-mediated cow's milk immediate hypersensitivity.<sup>8</sup> Whether allergen-specific IgE is expressed and plays a role in EoE is unknown. However, local IgE transcripts are present by PCR in the esophagus of subjects with EoE regardless of whether or not they are identified to be atopic.<sup>9</sup> Our observation of clinical tolerance of baked milk in a subset of patients with EoE supports a role for an IgE-mediated mechanism. Our results showed that baked milk is well tolerated in a subset of patients despite established CMME. The ability to add baked milk products back into the diet may improve compliance, quality of life, and nutrition in patients with CMME. Commonly used allergen testing modalities (skin prick testing, patch testing, and specific IgE testing) are not helpful in predicting the outcome of baked milk ingestion. Although promising, our study is limited by its retrospective nature and small sample size. Our results must be validated in a prospective study before generalized application in clinical practice.

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## REFERENCES

1. Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol* 2011;128:3-20.e6; quiz 21-2.

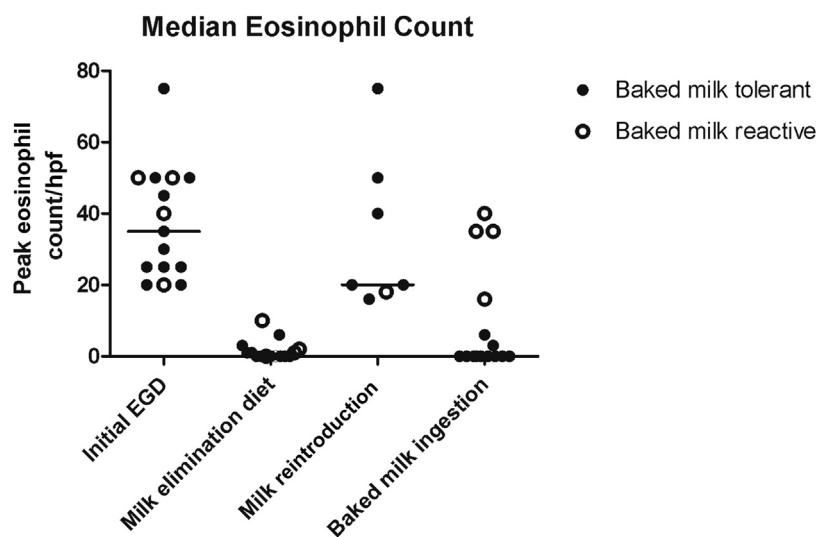
2. Kagalwalla AF, Shah A, Li BU, Sentongo TA, Ritz S, Manuel-Rubio M, et al. Identification of specific foods responsible for inflammation in children with eosinophilic esophagitis successfully treated with empiric elimination diet. *J Pediatr Gastroenterol Nutr* 2011;53:145-9.
3. Lucendo AJ, Arias Á, González-Cervera J, Yagüe-Compadre JL, Guagnozzi D, Angueira T, et al. Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: a prospective study on the food cause of the disease. *J Allergy Clin Immunol* 2013;131:797-804. Available at: <http://www.sciencedirect.com/science/article/pii/S0091674912026449>. [Accessed February 11, 2013].
4. Kagalwalla AF, Amsden K, Shah A, Ritz S, Manuel-Rubio M, Dunne K, et al. Cow's milk elimination: a novel dietary approach to treat eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 2012;55:711-6.
5. Medeiros LCS, Speridião PGL, Sdepanian VL, Fagundes-Neto U, Morais MB, et al. [Nutrient intake and nutritional status of children following a diet free from cow's milk and cow's milk by-products]. *J Pediatr (Rio J)* 2004;80:363-70.
6. Cummings AJ, Knibb RC, King RM, Lucas JS. The psychosocial impact of food allergy and food hypersensitivity in children, adolescents and their families: a review. *Allergy* 2010;65:933-45.
7. Nowak-Węgrzyn A, Bloom KA, Sicherer SH, Shreffler WG, Noone S, Wanich N, et al. Tolerance to extensively heated milk in children with cow's milk allergy. *J Allergy Clin Immunol* 2008;122:342-7.e2.
8. Nowak-Węgrzyn A, Fiochi A. Rare, medium, or well done? The effect of heating and food matrix on food protein allergenicity. *Curr Opin Allergy Clin Immunol* 2009;9:234-7.
9. Vicario M, Blanchard C, Stringer KF, Collins MH, Mingler MK, Ahrens A, et al. Local B cells and IgE production in the oesophageal mucosa in eosinophilic oesophagitis. *Gut* 2010;59:12-20.

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## Prevalence of self-reported food allergy in the National Health and Nutrition Examination Survey (NHANES) 2007-2010

### To the Editor:

Food allergy is a common condition, with widely varying estimates of prevalence worldwide and within the United States. The National Health and Nutrition Examination Survey (NHANES) is a periodic survey conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention that examines a nationally representative sample of approximately 5000 subjects each year. Further description of NHANES methodologies can be found in this article's Online



**FIG E1.** Median peak eosinophil count/hpf at different time points.